PACLitaxel 80 (7 day) and Trastuzumab (21 day) Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement Status
Adjuvant treatment of HER2 positive, node-negative breast cancer of tumour size ≤ 3cm	C50	00815a	N/A

* This is for post 2012 indications only.

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

PACLitaxel is administered weekly on Days 1, 8 and 15 of a 21 day cycle for 4 cycles (Cycles 1 to 4). Trastuzumab intravenous is administered at a dose of 8 mg/kg on Day 1 of the first cycle, followed by 6 mg/kg from Cycle 2 onwards. Trastuzumab can be substituted with the subcutaneous (SC) formulation where this has been approved locally.

Following completion of the first 4 cycles, treatment with trastuzumab monotherapy is continued to complete one year of trastuzumab therapy or until disease recurrence, whichever occurs first or unacceptable toxicity develops.

Facilities to treat anaphylaxis MUST be present when the systemic anti-cancer therapy (SACT) is administered.

Table 1: Treatment Schedule for PACLitaxel (IV) and Trastuzumab (IV)

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	**1**	Trastuzumab [a, b, c]	8mg/kg	IV infusion * Observe post infusion	250mL 0.9% NaCl over 90 minutes	Cycle 1
1	**1**	Trastuzumab [a, b, c]	6mg/kg	IV infusion * Observe post infusion	If no adverse reactions use 250mL 0.9% NaCl over 30 minutes	Every 21 days from Cycle 2 onwards
2	**1, 8, 15**	PACLitaxel [d, e]	80mg/m^2	IV infusion	250mL 0.9% NaCl over 1 hour	Every 21 days for 4 cycles
[a]Recommended Observation period: Patients should be observed for at least six hours after the start of the first infusion and for two hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms. Any deviation should be noted in local policies.						
[b]Trastuzumab is incompatible with glucose solution.						
[c]Trastuzumab can be substituted with the subcutaneous formulation where this has been approved locally. See Table 2 below.						
[d]PACLitaxel must be supplied in non-PVC containers and administered using non-PVC giving sets and through an in-line 0.22 µm filter with a microporous membrane.						
[e]PACLitaxel should be diluted to a concentration of 0.3-1.2mg/mL.						

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

*See alternative treatment schedule using SC trastuzumab below

ALTERNATIVE TREATMENT SCHEDULE

PACLitaxel 80 (IV) and Trastuzumab (SC) Therapy

Table 2: Alternative Treatment Schedule for PACLitaxel (IV) and Trastuzumab (SC)

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	**1**	Trastuzumab [a, b]	600mg	SC injection	Over 2-5 minutes	Every 21 days
2	**1, 8, 15**	PACLitaxel [c, d]	80mg/m^2	IV infusion	250mL 0.9% NaCl over 1 hour	Every 21 days for 4 cycles
[a] The injection site should be alternated between the left and right thigh. New injections should be given at least 2.5 cm from the old site and never into areas where the skin is red, bruised, tender, or hard. During the treatment course with trastuzumab subcutaneous formulation other medicinal products for subcutaneous administration should preferably be injected at different sites.						
[b] Patients should be observed for 30 minutes after the first injection and for 15 minutes after subsequent injections for signs or symptoms of administration-related reactions. Any deviation should be noted in local policies.						
[c] PACLitaxel must be supplied in non-PVC containers and administered using non-PVC giving sets and through an in-line 0.22 µm filter with a microporous membrane.						
[d] PACLitaxel should be diluted to a concentration of 0.3-1.2mg/mL.						

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

ELIGIBILITY:

- Indication as above
- HER2 overexpression or HER 2 gene amplification as determined by an accurate and validated assay. Please see *Recommendations on Reporting on HER2 Status in Breast Cancer Patients* here
- Tumour size less than or equal to 3 cm
- Patients should have a pre-treatment LVEF of ≥ 55%
- Many clinical trials have been conducted with LVEF ≥ 50%. Clinical judgment should be exercised where patients fall between these two ranges
- ECOG status 0-2
- Adequate organ function

EXCLUSIONS:

- Hypersensitivity to PACLitaxel, trastuzumab, murine proteins, hyaluronidase or to any of the excipients
- Clinically significant cardiac disease
- Baseline neutrophil count < 1.5 x 10^9/L
- Severe hepatic impairment

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Cardiac function (LVEF using ECHO or MUGA scan)

Regular tests:

- FBC, renal and liver profile
- Cardiac function (MUGA or ECHO) every 12 weeks. Where there are signs of cardiac impairment, four to eight weekly checks may be more appropriate

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.

Trastuzumab IV

- If the patient misses a dose of trastuzumab by one week or less, then the usual maintenance dose of 6mg/kg should be given as soon as possible. Do not wait until the next planned cycle. Subsequent maintenance doses should then be given according to the previous schedule.
- If the patient misses a dose of trastuzumab by more than one week, a re-loading dose of trastuzumab (8 mg/kg) should be given over approximately 90 minutes, at the discretion of the clinician. Subsequent trastuzumab maintenance doses (6 mg/kg) should then be given weekly from that point.

Trastuzumab SC

- If the patient misses a dose of subcutaneous trastuzumab, it is recommended to administer the next 600mg dose (i.e. the missed dose) as soon as possible. The interval between consecutive trastuzumab subcutaneous formulation administrations should not be less than three weeks.

Haematological:

Table 3: Dose modifications for PACLitaxel in haematological toxicities

ANC (x10^9/L)		Platelets	Dose	Dose after neutropenic sepsis
≥ 1.5	And	> 90	80mg/m^2	65mg/m^2
*1-1.49	Or	70-90	65mg/m^2	50mg/m^2
< 1	Or	< 70	Delay and reduce next dose to 65mg/m^2 or add G-CSF	Delay

* If the ANC is 1 to 1.49 and patient is fit and well can consider full dose of 80 mg/m^2 at discretion of prescribing Consultant

Renal and Hepatic Impairment:

Table 4: Dose modification of PACLitaxel and trastuzumab in renal and hepatic impairment

<table>
<tr><th>Drug</th><th colspan="2">Renal impairment</th><th colspan="4">Hepatic impairment</th></tr>
<tr><td rowspan="5">PACLitaxel [a]</td><td colspan="2" rowspan="4">No need for dose adjustment is expected.

Haemodialysis: No need for dose adjustment is expected.</td><th>ALT</th><th></th><th>Total bilirubin</th><th>Dose</th></tr>
<tr><td>< 10 x ULN</td><td>and</td><td>≤ 1.25 x ULN</td><td>No dose reduction</td></tr>
<tr><td>< 10 x ULN</td><td>and</td><td>1.26 - 2.0 x ULN</td><td>75% of original dose</td></tr>
<tr><td>< 10 x ULN</td><td>and</td><td>2.01 – 5.0 x ULN</td><td>50% of original dose</td></tr>
<tr><td>≥ 10 x ULN</td><td>and/or</td><td>> 5 x ULN</td><td>Contraindicated</td></tr>
<tr><td rowspan="4">Trastuzumab [b]</td><th>CrCl (mL/min)</th><th>Dose</th><td colspan="4" rowspan="4">No need for dose adjustment is expected</td></tr>
<tr><td>≥ 30 ml/min</td><td>No dose adjustment is needed</td></tr>
<tr><td>< 30 ml/min</td><td>No need for dose adjustment is expected</td></tr>
<tr><td>Haemodialysis</td><td>No need for dose adjustment is expected</td></tr>
<tr><td colspan="6">[a] PACLitaxel (renal and hepatic – Giraud et al 2023);
[b] Trastuzumab (renal and hepatic - Giraud et al 2023).</td></tr>
</table>

Management of adverse events:

Table 5: Dose modification schedule for PACLitaxel based on adverse events

Adverse reactions	Discontinue	Recommended dose modification
Grade 2 motor or sensory neuropathy		Decrease dose by 10mg/m^2
All other grade 2 non-haematological toxicity		Hold treatment until toxicity resolves to ≤ grade 1. Decrease subsequent doses by 10mg/m$^{2.}$
≥ Grade 3 reaction	Discontinue	

Table 6: Trastuzumab dose modification schedule based on adverse events

Adverse reactions	Discontinue	Recommended dose modification
LVEF drops ≥ 10 ejection fraction points from baseline and to below 50%		Withhold treatment. Repeat LVEF after 3 weeks. No improvement or further decline, discuss with consultant and consider referral to cardiology
Symptomatic heart failure		Consider discontinuation – refer to cardiology for review. Clinical decision.
NCI-CTCAE Grade 4 hypersensitivity reactions	Discontinue	
Haematological		Treatment may continue during periods of reversible, chemotherapy-induced myelosuppression. Monitor carefully for any complications of neutropenia.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic AntiCancer Therapy (SACT) Induced Nausea and Vomiting linked here

PACLitaxel: Low **(Refer to local policy)**
Trastuzumab: Minimal **(Refer to local policy)**

For information:
Within NCIS regimens, antiemetics have been standardised by Medical Oncologists and Haemato-oncologists and information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - link here
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - link here

PREMEDICATIONS:

- All patients must be premedicated with corticosteroids, antihistamines, and H_2 antagonists prior to first dose of PACLitaxel treatment.
- The H_2 antagonist, famotidine, can potentially be omitted from the premedication requirements for PACLitaxel but the risk of hypersensitivity with this approach is unknown.
    - Caution is advised particularly for patients receiving PACLitaxel every 3 weeks. It is recommended that if famotidine is omitted that patients are monitored closely for any signs of hypersensitivity. Any hypersensitivity should be managed as per local policy.
    - Where a patient experiences hypersensitivity, consider the use of alternative H_2 antagonists **(Refer to local policy).**

  Table 7 outlines suggested premedications prior to treatment with PACLitaxel.

Table 7: Suggested premedications prior to treatment with PACLitaxel

Day of treatment	Drug	Dose	Administration prior to PACLitaxel
Day 1	DexAMETHasone[a]	8mg IV	30 minutes
Day 1	Chlorphenamine	10mg IV	30 minutes
Day 1	Famotidine	20mg IV	30 minutes
Day 8[b] and thereafter	DexAMETHasone[a]	None	
Day 8 and thereafter	Chlorphenamine	10mg IV	30 minutes
Day 8 and thereafter	Famotidine[c]	20mg IV	30 minutes
[a]Dose of dexAMETHasone may be altered, in the event of hypersensitivity reaction, to 20 mg of dexAMETHasone orally 12 hr and 6 hour prior to re-challenge with PACLitaxel according to consultant guidance.			
[b]Dose of dexAMETHasone may be added from day 8 if increased risk or previous hypersensitivity reaction according to consultant guidance.			
[c]Dose of famotidine may be omitted in the absence of hypersensitivity reaction according to consultant guidance.			

OTHER SUPPORTIVE CARE:

- Prophylactic G-CSF may be used to mitigate the risk of haematological toxicities.
- Myalgias and arthralgias may occur with PACLitaxel. Analgesic cover should be considered.

ADVERSE EFFECTS:

Please refer to the relevant Summary of Product Characteristics (SmPC) for details.

DRUG INTERACTIONS:

Current SmPC and drug interaction databases should be consulted for more information.

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5. Perez A, Rodeheffer R. Clinical Cardiac Tolerability of Trastuzumab. J Clin Oncol 2004; 22:322-329.
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Version	Date	Amendment	Approved By
1	11/05/2023		Prof. Maccon Keane
2	14/06/2024	Reviewed. Added subcutaneous formulation. Table 2 added. Updated renal and hepatic dose modifications in line with Giraud et al, 2023. Updated in line with NCCP standardisation.	Prof. Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.